GUIDANCE[1]

GUANABENZ ACETATE TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Guanabenz acetate is a centrally active hypotensive agent. It appears to stimulate α_2-adrenergic receptors in the CNS and cause inhibition of sympathetic outflow from the brain (1-4).

Guanabenz is indicated in the treatment of hypertension and may be employed alone or in combination with a thiazide diuretic (1-5). It is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hepatic and/or renal impairment, with cardiovascular diseases, during pregnancy, and in geriatric patients (1-2).

The side effects or guanabenz are generally mild, and include dry mouth, drowsiness/sedation, dizziness, weakness, and headache (1-2). Abrupt withdrawal of guanabenz (especially at doses $\geq$ 32 mg/day) may cause a

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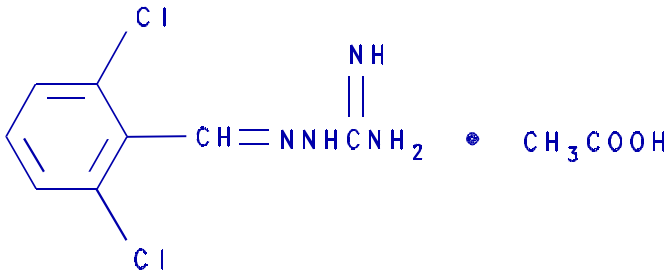
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

rapid increase in serum catecholamine concentrations and systolic and diastolic blood pressures (2).

Guanabenz acetate is currently marketed by Wyeth-Ayerst as Wytensin [R] in 4 mg and 8 mg tablets. The initial dosage is 4 mg twice daily and may be gradually increased to a maximum of 32 mg twice daily (1-2).

B. Chemistry

Guanabenz acetate, E-2,6-dichlorobenzylidene amino-guanidine acetate (molecular weight 291.14) has the following structure:



The drug has a pK_a of 8.1, and the solutions of guanabenz acetate have a pH of 5.5 - 7. Its solubilities in water and in alcohol at 25 °C are 11 and 50 mg/mL, respectively. It occurs as a white to off-white powder with not more than a slight odor. The drug product should be stored in tight, light-resistant containers at room temperature (2).

C. Pharmacokinetics

Following an oral dose of guanabenz acetate, about 75% of the drug is absorbed. Because of extensive first pass metabolism, the bioavailability is low (not established in man, but 20%-30% in monkeys, 2, 4, 6-7). A food effect on the drug absorption has not been determined (1-2, 7).

Guanabenz is rapidly and extensively distributed into the CNS (2) and various organs (11). Following a 16 mg dose to fasting healthy individuals, peak plasma levels of unchanged drug are only 2.4 - 2.7 ng/mL at 2 - 5 hours with about 90% bound to proteins (1-2, 4, 8).

For hepatic impaired patients, the Cmax is higher, 7.8 ng/mL, 8. From the limited studies in man, the concentration-time curves for the drug are best fit to a one- or two-compartment open model with a first-order absorption process and a lag time (5, 8). The apparent steady-state volume of distribution is about 93 and 147 L/kg after 16 and 32 mg oral doses, respectively (2).

Therapeutic effects begin within 1 hour and last over 10 hours with a peak around 2 to 4 hours. At usual clinical doses, effects appear to be linearly related to dose (9).

The elimination half-life of guanabenz averages 4-9 hours in healthy men (5, 8). For liver impaired or hypertensive patients, the half-life averages 12-14 hours (8, 10).

Guanabenz metabolites (mainly from liver) are excreted in urine (70-80% within 72 hours) and feces (10-30% in 6 days) (7, 10). Urinary metabolites include (E)-p-hydroxyguanabenz (11%), its glucuronide conjugate (25%), the Z-guanabenz (1.1%, the only active metabolite with about 25% parent drug activity), and 1.4% unchanged drug.

II. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

A. Product Information

1. FDA Designated Reference Product: Wytensin® (Wyeth Ayerst) 8 mg Tablet

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger .

[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Types of Studies Required

A randomized, single-dose, two-treatment, two-period, two-sequence crossover study under fasting conditions comparing an 8 mg tablet of generic guanabenz acetate test product with the reference product, Wytensin [R] 8 mg Tablet manufactured by Wyeth-Ayerst.

C. Recommended Protocol for Conducting a Fasted Single Dose Bioequivalence Study

Objective: To compare the rate and extent of absorption of a generic formulation with that of the reference formulation when given as equal labeled doses.

Design: The study design is a single dose two-treatment, two-period, two-sequence crossover with a washout period of at least one week between Phase I and Phase II dosing. Equal numbers of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical sites for the study should be identified along with the names, titles and curriculum vitae of the medical, scientific and analytical directors.

Selection of Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers 18 to 50 years of age and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results (hematology, blood chemistry, urinalysis). Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to guanabenz acetate should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the study.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 ml of water.

Restrictions: Study volunteers should observe the following restrictions:

a. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

b. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx medications beginning two weeks and no OTC medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: Venous blood samples should be collected pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 15, 24, 30, and 36 hours following dosing. Plasma should be separated promptly and immediately frozen until assayed.

Analytical Methods: Plasma guanabenz should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between days) (12-15). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and Q.C. chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data: See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design".

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

Subject Monitoring: Blood pressure and pulse rate should be monitored during the blood sampling periods. Any subject with a heart rate greater than 120 beats per minutes should have an electrocardiogram performed and have his pulse monitored hourly until resolved.

Retention of Samples: The laboratory conducting the bioequivalence testing should retain an appropriately identified reserve sample of the test product and the reference standard used to perform an *in vivo* bioequivalence study for approval of the application. Each reserve sample should consists of at least 200 dosage units. For more information on retention of bioequivalence samples, please refer to CFR 21,320.32.

III. *IN VITRO* TESTING REQUIREMENTS

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product. The bio-study lots should be used for those product strengths tested *in vivo*. The current official USP dissolution method should be followed and should be referenced by the sponsor. The following USP XXII method and tolerances are recommended:

Apparatus:	II (Paddle)
RPM:	50
Medium:	Water
Volume:	1000 mL
Sampling Times:	15, 30, 45, 60 Minutes
Tolerance (Q):	NLT 75% (Q) of Guanabenz is dissolved in 60 minutes
Analytical:	As per USP XXII, UV absorbance at about 272 nm

For each individual dosage unit, the following should be reported: Percent of label claim dissolved at each specified testing interval, the mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation).

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

IV. WAIVER REQUIREMENTS

Waiver of *in vivo* bioequivalence study requirements for the 4 mg strength of the generic product may be waived per 21 CFR 320.22(d)(2) provided both of the following conditions are met:

A. The 4 mg tablet is proportionally similar in both active and inactive ingredients to the 8 mg tablet which has demonstrated bioequivalence to a reference product *in vivo.*

B. The 4 mg and 8 mg tablets of the generic product meet the dissolution testing requirements.

V. REFERENCES

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Prepared by: _____ Date:_____
Beatrice P. Chen, Ph.D.
Division of Bioequivalence

Concur: _____ Date:
_____
Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

Concur: _____ Date:
_____
Roger L. Williams, M.D.
Director